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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,492	03/06/2002	Elizabeth S. Light	142/003/PCT	8768

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VENTANA MEDICAL SYSTEMS, INC.
ATTENTION: LEGAL DEPARTMENT
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/582,492	LIGHT ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008 and 12 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,17,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7, 17, 23, and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to the papers received 11/12/07 and 3/18/07. The amendments, declaration and remarks have been carefully considered but were not persuasive to place the application in condition for allowance for the reasons which follow in this office action. This action is FINAL.

2. Claims 1, 7, 17, 23, and 24 are pending. Claims 1, 7, and 23 have been amended, and claim 24 is new. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This newly added claim recites that fragments "are removed" by washing at particular conditions. However, it is not clear how this method limitation relates to the claimed

product. It is not clear if applicant is trying to limit the reagent of claim 24 such that must comprise only the removed fragments or the remaining fragments or both, or if applicant is simply stating an intended use of the claimed reagent.

5. Claims 7 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The limitation in claim 23 which requires the "proportion of total HPV DNA in the reagent that comprises nucleic acid fragments of the first genomic HPV DNA probe set and the proportion of total HPV DNA in the reagent that comprises nucleic acid fragments of the third genomic HPV DNA probe set are decreased relative to the proportions of the total HPV DNA in the reagent…" appears to represent new matter. The specification provides a single example within this claim, but the specification does not provide any discussion or contemplation of this broad general subspecies, namely any possible combination of reagents where the fragments of the first and third reagents are "decreased" at any possible level relative to the other reagents. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter.

Further, in claim 7, the recitation of "about" prior to the statement of the percentages of total HPV DNA in the reagent for each of the plurality of nucleic acid fragments appears to be new matter because the specification does not provide any basis for modifications that are "about" each of the recited percentages. Such a recitation encompasses percentages that are above and below the recited numbers, but the specification does not provide written description of "about 8.3%," for example, the specification only contemplates 8.3%.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 17, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to reagents for detecting human papilloma virus DNA in a cell sample, and set forth a reagent comprising a plurality of DNA probe sets to the cell sample, wherein the probe sets include genomic HPV DNA probe sets that comprise a plurality of labeled nucleic acid fragments prepared by labeling essentially the full-length genomic sequences of each of HPV types 16, 18, 31, 33, 35, and 51, and wherein the fragments detectably hybridize to the genomic sequences of HPV types 16, 18, 31, 33, 35, 51, 39, 45, 52, 56, 58, 59, 68, and 70, but do not detectably hybridize to the genomic sequence of types 42, 43, or 44.

The examples in the specification teach the preparation of a probes wherein plasmids containing the whole genome of HPV types 16, 18, 31, 33, 35, and 51 were labeled by nick translation with digoxigen dCTP (p. 8). The specification demonstrates that each of these individual probe reagents cross-hybridizes to some degree with other HPV types, some with other high risk types and some with other low risk types. For example, the HPV type 16 nick translated probe set detectably hybridized under the experimental conditions with types 6/11, 16, 31, 33, 35, 42, 43, 44, 51, and 58 (Example 1, p. 9). HPV types 6/11, 41, 42, 43, and 44 are all low risk types.

The specification describes a single combination reagent which consists of The "Present Probe Cocktail" which meets the functional limitations of the reagent recited in instant claim 1 and the other claims. The reagent is a combination of probes sets from 16, 18, 31, 33, 35, and 51 wherein the probe sets are present at particular concentrations relative to one another, namely those concentrations given in Table 2 on page 19 of the specification. However, the instant claims are much broader in nature than what is described in the specification with regard to what nucleic acid is required to be in the probe and how much of that nucleic acid.

The instant claims are quite broad with respect to the structural features of the reagent which are set forth in claim 1. The claims are quite broad with regard to the composition of the reagent used in the claimed method. The claims clearly require probe that was prepared by labeling essentially the full length genomic sequence of HPB types 16, 18, 31, 33, 35, and 51, but are inclusive of these probe sets at any concentration relative to one another, and further are inclusive of additional probe sets within the reagent, since the reagent is described using "comprising" language.

Claim 23 sets forth general requirements that HPV types 16 and 31 have lower representation in the probe reagent than the other listed types, but this disclosure is still quite broad in nature since it allows for any possible proportions within this generic requirement.

The specification suggests that the probes at equal value would not meet the limitations of the instant claims, and the specification teaches a single example of concentrations that would meet the limitations of the instant claims.

It is clear that the specification describes that a method which uses combination reagent which was comprised of different proportions of the individual HPV types- namely it contained 8.3% HVP 16 and 31 nick-translated DNA and 20.8% of each of HPV 18, 33, and 51 nick-translated DNA. However, the specification does not provide any additional reagents where the proportions of HPV types vary within the reagent or reagents which meet the functional requirements of the claims.

Additional dependent claims included in the rejection recite additional method steps which do not further describe the probe set used in the claimed invention.

The specification does not provide any description of the critical features of the single disclosed probe set which allow it to hybridize in the fashion described in the specification- namely that it hybridizes to the genomic sequences of HPV types 16, 18, 31, 33, 35, and 51, and additionally to types 39, 45, 52, 56, 58, 59, 68, and 70, except to teach that this functionality was achieved only when the probes were present at the concentrations given in table 2. Therefore, there is no description of how the single disclosed probe reagent could be modified and still retain the feature that applicant purports in the arguments and claims to be critical to the invention.

> Applicant is clearly in possession of a probe set that comprises probes that were produced by nick-translation of the full length genome of six separate plasmids, with one plasmid containing the whole genome of a HPV type and the six types being 16, 18, 31, 33, 35, and 51, wherein types 18, 33, 25, and 51 are present at 0.5 nanograms per milliliter of solution and types 16 and 31 are present at 0.2 nanograms per milliliter of solution (see p. 13, example 3).
> A has express possession of only one species in a genus which comprises many, many

different possibilities.

With regard to the written description, all of these claims encompass reagents comprising nucleic acid sequence different from those disclosed in the specific reagents which for which no written description is provided in the specification.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only a single reagent meeting the functional limitations of the claims is described, yet hundreds of thousands of possible reagents are encompassed by the claims. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of reagents modified from the single example given but possessing the functional characteristics required by the claims.

7. Claims 1, 17, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification, while being enabling for the reagent set forth in claim 7,, does not provide enablement reagents that have different proportions of HPV probes present yet still retain the functional properties of the reagents required as set forth in the claims.

The scope of the claims and the teachings in the specification are discussed in the written description rejection.

The prior art provides a wide variety of teaching regarding HPV cocktail probes. The prior art reference of Nuovo (1998) teaches an HPV consensus probe that hybridizes to HPV types 16, 18, 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 70, but not HPV type 6, 11, 42, 43, and 44. In this reference, HPV 70 is considered a "high risk" type. Nuovo et al. do not disclose any information about the content of the consensus probe, and applicant argues in the remarks filed 11/20/06 that the reference does not provide enabling disclosure of the reagent because the composition of the consensus probe is not provided, and thus, using the reference, a person of ordinary skill in the art would not be able to determine the particular HPV types or proportions of the particular HPV types without undue experimentation. The disclosure differs from the instant claims and disclosure because the instant specification teaches a reagent which comprises probes produced by nick-translation from six particular HPV types. The specification teaches that when these nick-translation products are combined in a very particular ratio, results identical to those provided by Nuovo (1998) are obtained. There is no disclosure in the

specification of additional probe reagents. Following applicant's reasoning set forth in the declaration by Gerard J. Nuovo and in the arguments provided by applicant, it would require undue experimentation for one of ordinary skill in the art to modify the specific reagent taught in the specification to arrive at a reagent that meets the functional limitations of the claims. First, as noted, the single disclosed cocktail does not meet the limitations set forth in the claims. Second, even if it did, determining additional reagents which meet these limitations would require extensive experimentation and screening of samples using reagents with differing compositions- where the content of the probe sequences in the reagent were varied, where the concentrations of relative HPV types were varied, indeed, where the HPV types themselves included within the reagent were varied.

Applicant states in their declaration "Using the teachings of my 1998 reference and knowledge in the art at the time my 1998 reference was published, a person of ordinary skill in the art…would not be able prepare a high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of low-risk HPV type."

The instant specification does not provide any further guidance as to how the single disclosed embodiment could be modified and arrive at a probe set that functions in the same way. The specification does not provide additional guidance. As noted by the declaration and applicant's arguments, it is highly unpredictable which formulations of the probe sets will cross-hybridize with the low-risk HPV types. Indeed, applicant's specification demonstrates this unpredictability since the preferred cocktail hybridizes in some instances with the low-risk types. Thus, in light of all of the evidence on the record, it is concluded that it would require undue experimentation to make and use the claimed invention.

Response to Remarks

Applicant points out that the examiner rejected claim 3 in the office action mailed 6/11/07, but that this claim was not pending at the time of the writing of that office action. Applicant is correct, and the inadvertent inclusion of claim 3 has been corrected in this office action. Applicant states on page 5 of the paper filed 11/12/07 that claim 24 was added prior to the previous office action. This statement is in error. Prior to the previous office action which was mailed 6/11/07, claim 23 was the final claim pending.

The rejection under 112 2nd paragraph is overcome by the amendment to the claims.

The rejection of claim 1, 17, and 23 for under 112 1st paragraph for new matter is overcome by amendment to the claims.

Applicant traverses the new matter rejection insofar as it would be applied to amended claim 23, stating that support for this limitation can be found in the specification's disclosure that undesired cross-reactivity observed with genomic HPV DNA probes prepared from the genomic sequences of HPV types 16 and 31 can be essentially nullified by reducing the concentration of these two genomic HPV DNA probes in the probe reagent, pointing to page 9, lines 8-10, page 10, lines 5-8, and tables 1 and 3. However, applicant's characterization generalizes what the specification actually teaches. For example, at page 9, in the final paragraph, the specification states, "Since some undesired cross-reactivity was noted with probes to HPV type 16 and 31, the concentration of these two was lowered in the probe reagent to compensate. The percentages of each genomic probe in the DNA cocktail are given in Table 2." Table 2 of the specification gives only one particular set of percentages which were used to achieve the desired results of

cross-reactivity combined with no hybridizing to non-desired types. The section of the specification does not generally suggests that any change in proportions would work, or even that there are a variety of possible proportions that would be functional or that are contemplated. The specification teaches that the concentrations were lowered, and that they were lowered to a particular value.

Applicant points out on page 8 of the remarks that the specification provides the first teaching in the art that the concentration of genomic sequences of HPV types 16 and 31 must be lowered in order to eliminate undesired cross-reactivity, as noted in the inventor's declaration.

Applicant states that in view of the teaching of the specification the skilled artisan would recognize that the concentrations of the genomic sequences must be lowered, and that the undesired cross-reactivity could be eliminated using reagents other than those depicted in table 2. This position is supported in the declaration. First, it is noted that the declaration is an opinion declaration provided by an inventor in this application. There is no support for the opinion given therein by factual evidence. Nonetheless, the question of possession is different from that of enablement or obviousness. In this case, the claim remains rejected for new matter because there was no contemplation or suggestion in the specification commensurate in scope with the reagents that are now claimed in claim 23.

Applicant's arguments regarding claim 7 are duplicative of those set forth for claim 23 and are previously addressed.

Applicant's comments regarding the meaning of "essentially the full-length genomic sequence" on pages 11 and 12 are noted. The aspect of the rejections that might have been relevant to this language has been removed.

Applicant's discussion of claim 7 on page 13 of the remarks are moot because this claim is no longer rejected for lack of written description, other than the new matter rejection. If the word "about" were removed from this claim in parts (a)-(f), this claim would be allowable.

The discussion which states that the genomic HPV DNA probes are defined only by function has been removed in view of the amendment to the claims.

On page 14 of the remarks applicant addresses the "Critical features of cross-reactivity." Applicant states that the specification discloses that the undesired cross-reactivity observed can be essentially nullified by reducing the concentration of these two genomic probes in the probe reagent. As previously noted, however, the specification does not provide any guidance as to how the exemplary concentrations given in the specification can be modified while still retaining the critical property of maintaining the desired cross-reactivity and eliminating the undesired cross-reactivity.

Applicants suggest that with regard to written description they merely need to communicate to those skilled in the art that the claimed subject matter is obvious over their disclosure. The examiner disagrees. The court has made it clear that with regard to chemical compounds, the standard for written description is possession, not enablement or intent to claim. "While we have no doubt a person so motivated would be enabled by the specification to make it, this is beside the point for the question is not whether he would be so enabled but whether the specification discloses the compound to him, specifically, as something appellants actually invented. We think it does not." In Re Ruschig, 379 F.2d 990, 995, 154 U.S.P.Q. 118, 123 (CCPA 1967). Furthermore, the court stated "Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a

description of that material." The Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q.2d 1406 (Federal Circuit 1997). In the instant case, however, applicant has not even discussed or suggested variation in the concentration of probes in the reagent of the present invention, nor have they provided any guidance as to how to change the specific reagent given in the specification yet still arrive at a reagent within the functional limits of the one set forth in the claim.

The rejection for lack of written description is maintained.

Applicant argues that the instant specification provides more guidance than the prior art, namely an exemplary reagent and the teaching that cross-reactivity can be nullified by reducing the concentration of the two genomic HPV DNA probes in the reagent. However, the claims are very broad in nature, and encompass using additional probes in the reagent as well as the recited probes present at a wide variety of possible concentrations. There is no guidance in this unpredictable art, however, as to how to arrive at additional reagents. There is no guidance as to how the single working example might be modified.

Applicant disagrees that one of ordinary skill would vary the content of the probe sequences, the proportions of the genomic probes sets, and the HPV types included within the reagent. Applicant states that the particular HPV types required for the reagent are explicitly recited in the claims. The minimum is recited, but additional probe types are clearly encompassed by the use of the transitional phrase "comprising." Applicant states that one would not have to vary the content of the probe sequences or the proportions of the HPV genomic probe sets. However, to practice the invention commensurate in scope with the claimed invention, each of these are required as the independent claim is sufficiently broad so as to

encompass the use of a wide variety of reagents. The issue is the scope of the claim. Clearly, there is one enabled embodiment given in the specification and noted in the rejection.

Applicant disagrees that there is no guidance in the specification as to how to modify the "Present Probe Cocktail" and still arrive at other embodiments of methods within the scope of the claimed invention, but none of the teachings of the specification pointed to by applicant do provide this guidance. The specification suggests that equal amounts of probe would not work and that the particular reagent given would work, but the specification is silent as to what other reagents might work. Applicant repeatedly refers to the specification as teaching that "undesired cross reactivity can be nullified" but as noted, the portion of the which makes this statement is not generic as applicant suggests but is followed by the very specific teaching of the proportions of the present probe cocktail.

The rejection is maintained.

Conclusion

8. No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the

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/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

June 3, 2008